UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,241	08/31/2006	Ichiro Iwai	053466-0450	9322

22428 7590 12/19/2008

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER
KOSAR, AARON J

ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
12/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,241	IWAI ET AL.	
	Examiner	Art Unit	
	AARON J. KOSAR	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) *3 and 4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/31/06; 5/9/07; 6/12/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of Group I, claims 1-2, in the reply filed on September 13, 2008 is acknowledged. Claims 3-4 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. The election/restriction requirement is still deemed proper and therefore made final.

Claims 1-4 are pending of which **claims 1-2** are pending and have been examined to the extent of the elected invention.

Information Disclosure Statement (IDS)

The information disclosure statements (IDS) submitted on 8/30/2006, 5/9/2007, and 6/12/2007 have been considered by the Examiner; however, it is noted that the IDS contains references that are in a foreign language. The relevant portions of 37 CFR § 1.98 (a) and (b) state:

(a) Any information disclosure statement filed under § 1.97 shall include the items listed in paragraphs (a)(1), (a)(2) and (a)(3) of this section...
(2) A legible copy of:
(i) Each foreign patent;
(ii) Each publication or that portion which caused it to be listed, other than U.S. patents and U.S. patent application publications unless required by the Office;
(iv) All other information or that portion which caused it to be listed.
(3)(i) A concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent, publication, or other information listed that is not in the English language. The concise explanation may be either separate from applicant's specification or incorporated therein.
(ii) A copy of the translation if a written English-language translation of a non-English-language document, or portion thereof, is within the possession, custody, or control of, or is readily available to any individual designated in § 1.56(c).
(b)(4) Each foreign patent or published foreign patent application listed in an information disclosure statement must be identified by the country or patent office which issued the patent or published the application, an appropriate document number, and the publication date indicated on the patent or published application.
(5) Each publication listed in an information disclosure statement must be identified by publisher, author (if any), title, relevant pages of the publication, date, and place of publication.

Accordingly, the references have been considered to the extent presented in the English language; as presented and accompanied by reference document which is an English language equivalent or translation, to the extent cited in the instant Application's disclosure, or as cited by the Examiner in a PTO-892.

References which have been considered have been initialed as indicated on the IDS. References which have not been considered or which have been cited in duplicate on the IDSs have been lined through.

Specification

The disclosure is objected to because of the following informalities:

On page 10, line 18, the phrase "ascorbic acid or vitamin," appears to be an inadvertent or typographical error of the phrase -- ascorbic acid or vitamin C, --.

On page 11, line 2, 18, and 30 and page 12, line 6, the term "Skincon-200" appears to be a typographical error of the Tradename -- SKICON-200 --.

(cf. see ***U****:PTO-892: IBS "Company Profile" retrieved December 4, 2008 from <http://66.102.1.101/translate_c?hl=en&sl=ja&u= http://www.ibs-hamamatsu.co.jp/english/company.html&prev=/search%3Fq%3Dibs%2Bhamamatsu%26hl%3Den%26rls%3DGGLD,GGLD:2004-30,GGLD:en&usg=ALkJrhgdohzfXMZLvwl 2Zau8k19QBZuiyg>, 2 pages.)*

On page 7, lines 12-13, the term "Scotch Superstrength Mailing Tape" appears to be a typographical error of the term -- SCOTCH® SUPER STRENGTH MAILING TAPE --.

Please note, the use of trademarks/tradenames ***should be capitalized wherever they appear****. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.*

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 1 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is rejected because the claims may be broadly and reasonable interpreted as embracing naturally-occurring compositions and processes (e.g. aged/desquamating skin).

Please note, however, this ground may be overcome by amending the claim to recite compositions or active steps which would clearly and unambiguously distinguish the instantly claimed process and composition therein from naturally-occurring compositions/processes.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 2 are incomplete for omitting essential steps. While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practiced. The minimum requirements for method steps minimally include a *providing/contacting step* in which the reaction of the sample with the reagents necessary for the reaction/process are recited, a *detecting/effecting step*

in which the reaction steps are quantified or visualized, and a *correlating/concluding step* describing how the results of the method allow for the determination.

In these claims, claim 1 recites a use without setting forth an active, positively recited method step (*cf.* see claim 1, US 5,749,847 (**A**:PTO-892). Claim 2 provides for a stratum corneum sample and the steps of labeling and detecting; however, the method recites a method for "evaluating the transparency and or water-holding capacity of a stratum corneum" for which the claims do not recite a correlating/concluding step describing how one would arrive at a transparency or water-holding evaluation.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for measuring conductance and fluorescence intensity of oxidized proteins, does not reasonably provide enablement for water-holding capacity or all modes of transparency to the extent instantly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (Wands, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the

breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to evaluating transparency and water-holding capacity of stratum corneum, including detecting fluorescence. The specification discloses the measurement of conductance of acrolein- or hypochlorous acid -treated skin and the transparency of acrolein-treated skin. Thus the claims taken together with the specification imply a breadth that is greater than is supported by the specification.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The state of the art is such that the UV-absorptive spectral properties (transparency) of proteinaceous and amino acid-containing compositions are known, which as taught by GOLDFARB, are dependent upon the amino acid extinction coefficients at specific wavelengths, wherein Goldfarb teaches "it is estimated that each peptide bond contributes as average of about 2500 to 2800 to the molar absorption coefficient" (**V**:PTO-892: table III and page 404, ¶1 : Goldfarb, et al. "The Ultraviolet Absorption Spectra of Proteins", The Journal of Biological Chemistry, 1951, 193 (1), pages 397-404.)

GILLIES (**V-1**:PTO-892: Gillies, R., et al. "Fluorescence Excitation Spectroscopy Provides Information About Human Skin In Vivo" J. Invest. Dermatol. 2000, 115, 704–707.) teaches that skin and stratum corneum fluorescence is known (e.g. Abstract; figure 2).

Also, as evidenced by IWAI (**X**:PTO-892: Iwai, I, et al. "Protein carbonyls damage the water-holding capacity of the stratum corneum" Skin Pharmacol. Physiol. 2008, 21(5), pages

269-73.), "protein carbonyl, including acrolein-protein adduct, has been observed in the skin. However, the influence of protein carbonylation on the stratum corneum (SC) *has not yet been clarified*." (Abstract, emphasis added).

Furthermore, as evidenced by RICHERT (**U-1**:PTO-892: Richert, S., et al. "Assessment of Skin Carbonyl Content as a Noninvasive Measure of Biological Age" Archives of Biochemistry and Biophysics 2002, 397(2), pp. 430–432.) "The oxidative modification of proteins by reactive species, especially reactive oxygen species, is implicated in the etiology or progression of a panoply of disorders and diseases" (Abstract, page 430) but that "that measurement of protein carbonyl in desquamating skin cells *does not provide a useful assessment of biological age*." (page 432, emphasis added).

Since the effect of protein carbonylation on the stratum corneum was not resolved at the time of the invention, then the effect of the protein carbonylation or selective/fluorescent labeling of the oxidized carbonyl groups therein remains largely unsolved and thus means for evaluating transparency/water-holding capacity or the myriad of modes of an oxidized protein/carbonyl functioning as an "indicator" is highly unpredictable to the extent claimed.

(5) The relative skill of those in the art:

The relative skill of those in the art is low to the extent of labeling compositions and measuring fluorescence thereof. The relative skill in the art is also low with respect to the species of hydrazine-labeling of oxidized proteins in stratum corneum. However, with respect to the *a priori* knowledge of the selective binding of all fluorophores capable of functioning in the claimed manner *and* capable of indicating all possible modes of transparency or functioning as a biomarker of water-holding capacity or transparency to the extent claimed, is beyond the

purview of one of skill except to the extent of the species disclosed in the prior art and as evidenced by IWAI (***X***) (*supra*).

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided a limited amount of direction as to the modes of spectral analysis and observation and the identity/species of compound employed to label oxidized protein. The specification has also provided examples of standard-addition of acrolein-oxidation treatment as dose-dependent effect upon conductance and alleged fluorescence intensity; however, the specification does not provide direction as to how one would arrive at a conclusion of transparency or water-holding capacity from fluorescence detection *per se* or from oxidized protein *per se*.

Additionally, from the image and description of Figure 5 (page 4, line 18-20; page 12, Experiment 5; Figure 5). the mode of "transparency" and how the sample was "observed" (e.g. visible/bright field/phase-contrast/polarized, fluorescence, confocal, etc. and optionally the wavelength(s) of light provided/observed therein) is unclear, although appears to be a critical feature of the invention.

The specification does not provide a sufficient number of working examples or guidance to support the genus of detecting and indicating; the myriad of labels/indicators/fluoro-phores; and the genus of possible conclusions of evaluations/determinations therefrom.

(8) The quantity of experimentation necessary:

Considering the state of the art and the high unpredictability and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to make and use the invention to the extent instantly claimed.

It is the Examiner's position that one skilled in the art could not practice the invention commensurate in the scope of the claims without undue experimentation.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names *joint inventors*. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1 is rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over GIRARD (**W**:PTO-892: Girard, P. et al. "A New Method for Assessing, *in vivo* in Human Subjects, the Basal or UV-Induced Peroxidation of the *Stratum corneum*", Current Problems in Dermatology, 1998, 26, pp. 99-107.) or .

The cited reference discloses a method comprising composition comprising skin stratum corneum fluorescent detection to indicate UV-induced oxidation/peroxidation thereof. The method of GIRARD (**W**) appears to be identical to the presently claimed composition since it

provides an indicator of stratum corneum. Consequently, the claimed method, which is drawn to using stratum corneum oxidized protein as an indicator, appears to be anticipated by the reference.

In the alternative, even if the composition (with respect to some undisclosed feature) is not identical to the referenced composition, with regard to some unidentified characteristics, the differences between that which is claimed and that which is disclosed, is so slight that the referenced method is likely to inherently provide the same characteristics as that of the claimed method, particularly in view of the similar characteristics which they have been shown to share (e.g. stratum corneum, oxidation, and fluorescence). Thus, the claimed method and compositions therein would have been obvious to those of ordinary skill in the art within the meaning of 35 USC § 103(a).

Accordingly, the claimed invention as a whole was at least *prima facie* obvious, if not anticipated by the reference, especially in the absence of sufficient, clear, and convincing objective evidence to the contrary.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by RICHERT (**U-1**:PTO-892) or GILLIES (**V1**-PTO-892) or SANDER (IDS: J. Invest. Dermatol., 2002) or THIELE (IDS: J. Invest. Dermatol., 1999).

RICHERT anticipates the claim by teaching assessing (evaluating) protein carbonyl content as a measure of assessing skin non-invasively. Richert further teaches measuring protein carbonylation spectrophotometrically following derivatization with 2,4-dinitophenylhydrazine (DNP) (e.g. page 431, ¶3; figure 1).

GILLIES anticipates the claim by teaching fluorescence excitation of skin and skin components, including stratum corneum, and samples *in vivo* and *ex vivo*. Gillies attributes the fluorescence to tryptophan and tyrosine fluorophores present in the tissue (e.g. figure 1, 2(a) and(d)).

SANDER anticipates thee claim by teaching measuring protein oxidation by labeling oxidized protein with DNPH, including labeling with rabbit anti-DNP antibody and anti-rabbit goat IgG-peroxidase (e.g. page 619, ¶6 and 12).

THIELE anticipates the claim by teaching protein carbonyl detection by labeling via a 2,4-dinitrophenylhydrazone derivative by reacting a stratum corneum with DNPH. Thiele also teaches photo-oxidation of stratum corneum with UV radiation and chemical oxidation with hypochlorite and peroxide (benzoyl peroxide) to provide increased cabonylation, including the oxidation of keratin 10 (e.g. Abstract; figures 2 and 3); page 336, right column, ¶1; page 337, "Discussion", ¶1 through page 338, ¶2).

Allowable Subject Matter

The following claims, drafted by the Examiner, is presently considered to distinguish patentably over the art of record in this application were such claims to be presented and if further supported by sufficient objective evidence, including any evidence submitted under 37 CFR §1.132, as to the identity of the "transparency" of figure 5 (*cf.* 35 USC 112, 1st ¶, above). Also please note, the Office presently renders the images in grayscale and thus any arguments of image coloration or implied compounds therein, to be complete should also reference the correlation to the grayscale rendering of the image of figure 5:

1. A method of determining the degree of protein oxidation in a skin sample comprising stratum corneum, the method comprising:

(a) providing a skin sample (S) selected from the group comprising:

(i) stratum corneum having carbonylated protein; or

(ii) oxidized stratum corneum, wherein the oxidized stratum corneum is obtained by contacting a skin sample comprising stratum corneum with an oxidizing agent and wherein the oxidizing agent comprises acrolein, thereby forming an acrolein-protein adduct;

wherein the skin sample (S) comprising said stratum corneum (i) or said oxidized stratum corneum (ii) is contacted and fluorescently labeled with a hydrazine fluorophore, the hydrazine fluorophore selected from the group comprising fluorescein-thiosemicarbazide; Texas Red hydrazide; biotin hydrazide reacted with fluorescein avidin; dintrophenylhydrazine (DNPH) reacted with anti-DNP antibody and with a fluorescein-labeled secondary antibody specific to the anti-DNP antibody; and DNPH reacted with a fluorescent dye;

(b) measuring the fluorescence of the skin sample (S); and then

(c) determining the degree of protein oxidation of the skin sample (S),

(i) wherein the fluorescence intensity of the skin sample (S) is indicative of the degree of protein oxidation in the skin sample (S);

(ii) wherein, relative to the fluorescence intensity of a skin sample not treated with acrolein (S'), an increased fluorescence intensity of the skin sample (S) indicates an increased protein oxidation in the skin sample (S); and

(iii) wherein said skin sample (S) has increased protein oxidation.

2. The method of claim 1, further comprising:

(d) measuring the conductance of a skin sample (S") comprising stratum corneum, wherein the skin sample (S") is oxidized by contacting with an oxidizing agent, wherein said

oxidizing agent is selected from the group comprising hypochlorous acid and acrolein, and wherein an increase in protein oxidation provides a decrease in conductance of the skin sample (S") relative to the conductance of a skin sample not contacted with an oxidizing agent (S').

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AARON J. KOSAR whose telephone number is (571)270-3054. The examiner can normally be reached on Monday-Thursday, 7:30AM-5:00PM, ALT. Friday,EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sandra Saucier/
Primary Examiner, Art Unit 1651

/Aaron J Kosar/

Examiner, Art Unit 1651